

WHAT IS CLAIMED IS:

1. A substantially hydrophilic conjugate comprising an analgesic peptide that is either biphalin or [D-Pen2, D-Pen5] enkephalin (DPDPE) covalently linked to a water soluble, nonpeptidic polymer selected from the group consisting of poly(ethylene glycol), copolymers of ethylene glycol and propylene glycol, poly(vinyl alcohol), poly(alkylene oxides), poly(oxyethylated polyols), poly(olefinic alcohols), poly(acryloyl morpholine), poly(vinyl pyrrolidone), poly(oxazoline), dextran, poly(hydroxyethyl methacrylate), wherein said conjugate, when administered into the blood circulation of a mammal, can transport across the blood-brain barrier.
2. The conjugate of Claim 1, which when administered in the blood circulation of a mammal, has an extended duration of analgesic effect as compared to the native peptide.
3. The conjugate of Claim 1 wherein said water-soluble, nonpeptidic polymer is further characterized by the absence of lipophilic moieties.
4. The conjugate of Claim 1 further characterized in that said nonpeptidic polymer and said peptide are conjugated in a reaction mixture in which the polymer and peptide are present as reagents.
5. The conjugate of Claim 1 further characterized by the absence of noncovalent bonds.
6. The conjugate of Claim 1, wherein said peptide is covalently linked to at least one terminus of said polymer.
7. The conjugate of Claim 1, wherein said peptide is covalently linked at one of its N-termini to said polymer.
8. The conjugate of Claim 1, wherein said water-soluble, nonpeptidic polymer is polyethylene glycol or a copolymer of polyethylene glycol and polypropylene glycol.

9. The conjugate of Claim 1, wherein said water-soluble, nonpeptidic polymer is polyethylene glycol.
10. The conjugate of Claim 9 wherein said polyethylene glycol is selected from the group consisting of monomethoxypolyethylene glycol, branched polyethylene glycol, polyethylene glycol with degradable linkages in the backbone, homobifunctional polyethylene glycol, heterobifunctional polyethylene glycol, multi-arm polyethylene glycol, pendant polyethylene glycol, and forked polyethylene glycol.
11. The conjugate of Claim 1, wherein said peptide is conjugated to at least one polyethylene glycol molecule.
12. The conjugate of Claim 1, wherein said biphalin has two polyethylene glycol moieties covalently attached.
13. The conjugate of Claim 1 wherein said nonpeptidic polymer is polyethylene glycol having a nominal average molecular weight of about 200 daltons to about 100,000 daltons.
14. The conjugate of Claim 13 wherein said polyethylene glycol has a nominal average molecular weight of about 1000 daltons to about 40,000 daltons.
15. The conjugate of Claim 13, wherein said polyethylene glycol has a nominal average molecular weight of 2000 daltons.
16. A pharmaceutical composition comprising a conjugate according to Claim 1 and a pharmaceutically acceptable carrier.
17. The conjugate of Claim 1 further comprising a neuroactive agent, which may be the same or different from said peptide, conjugated to said non-peptidic polymer.
18. The conjugate of Claim 1 further characterized by a dumbbell structure and further comprising a neuroactive agent, which may be the same or different from said peptide, conjugated to said nonpeptidic polymer.

19. The conjugate of Claim 1 further comprising doxorubicin or an imaging agent conjugated to said nonpeptidic polymer.

20. A substantially hydrophilic conjugate comprising an analgesic peptide covalently linked to a water soluble, nonpeptidic polymer in a reaction mixture in which said peptide and said nonpeptidic polymer are present as reagents, and wherein said polymer is selected from the group consisting of poly(ethylene glycol), copolymers of ethylene glycol and propylene glycol, poly(vinyl alcohol), poly(alkylene oxides), poly(oxyethylated polyols), poly(olefinic alcohols), poly(acryloyl morpholine), poly(vinyl pyrrolidone), poly(oxazoline), dextran, poly(hydroxyethyl methacrylate), said conjugate is characterized by the absence of noncovalent bonds and can transport across the blood-brain barrier of a mammal, said nonpeptidic polymer is characterized by the absence of lipophilic moieties, and wherein said peptide is selected from the group consisting of dynorphin A, enkephalins, double enkephalins, and endorphins.

21. A substantially hydrophilic conjugate comprising an analgesic peptide that is either biphalin [D-Pen2, D-Pen5] or enkephalin (DPDPE) covalently linked to a water soluble, nonpeptidic polymer in a reaction mixture in which said peptide and said nonpeptidic polymer are present as reagents, and wherein said polymer is selected from the group consisting of poly(ethylene glycol), copolymers of ethylene glycol and propylene glycol, poly(vinyl alcohol), poly(alkylene oxides), poly(oxyethylated polyols), poly(olefinic alcohols), poly(acryloyl morpholine), poly(vinyl pyrrolidone), poly(oxazoline), dextran, poly(hydroxyethyl methacrylate), said conjugate is characterized by the absence of noncovalent bonds and, when administered into the blood circulation of a mammal, can transport across the blood-brain barrier of a mammal, wherein said nonpeptidic polymer is absent lipophilic moieties.

22. A hydrophilic conjugate comprising an analgesic peptide that is either biphalin or [D-Pen2, D-Pen5] enkephalin (DPDPE) covalently linked to a water soluble, nonpeptidic polymer is selected from the group consisting of poly(ethylene glycol), copolymers of ethylene glycol and propylene glycol, poly(vinyl alcohol), poly(alkylene oxides), poly(oxyethylated polyols), poly(olefinic alcohols), poly(acryloyl morpholine),

poly(vinyl pyrrolidone), poly(oxazoline), dextran, poly(hydroxyethyl methacrylate), wherein said conjugate, when administered into the blood circulation of a mammal, can transport across the blood-brain barrier.

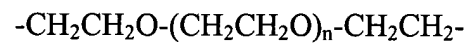
23. The conjugate of Claim 22 wherein said peptide is biphalin.

24. The conjugate of Claim 23 wherein said peptide is DPDPE.

25. A hydrophilic conjugate comprising an analgesic peptide covalently linked to a water soluble, nonpeptidic polymer in a reaction mixture in which said peptide and said nonpeptidic polymer are present as reagents, and wherein said polymer is selected from the group consisting of poly(ethylene glycol), copolymers of ethylene glycol and propylene glycol, poly(vinyl alcohol), poly(alkylene oxides), poly(oxyethylated polyols), poly(olefinic alcohols), poly(acryloyl morpholine), poly(vinyl pyrrolidone), poly(oxazoline), dextran, poly(hydroxyethyl methacrylate), said conjugate is characterized by the absence of noncovalent bonds and can transport across the blood-brain barrier of a mammal, said nonpeptidic polymer is characterized by the absence of fatty acids and glycolipids, and wherein said peptide is selected from the group consisting of dynorphin A, enkephalins, double enkephalins, and endorphins.

26. A hydrophilic conjugate comprising an analgesic peptide that is either biphalin [D-Pen2, D-Pen5] or enkephalin (DPDPE) covalently linked to a water soluble, nonpeptidic polymer in a reaction mixture in which said peptide and said nonpeptidic polymer are present as reagents, and wherein said polymer is selected from the group consisting of poly(ethylene glycol), copolymers of ethylene glycol and propylene glycol, poly(vinyl alcohol), poly(alkylene oxides), poly(oxyethylated polyols), poly(olefinic alcohols), poly(acryloyl morpholine), poly(vinyl pyrrolidone), poly(oxazoline), dextran, poly(hydroxyethyl methacrylate), said conjugate is characterized by the absence of noncovalent bonds and, when administered into the blood circulation of a mammal, can transport across the blood-brain barrier of a mammal, wherein said nonpeptidic polymer is absent fatty acids and glycolipids.

27. The conjugate of Claim 1 wherein said non-peptidic polymer is poly(ethylene glycol) having the general formula



wherein n ranges from about 10 to 2000.